REMARKS

Claims 1-24, of which claims 2-4 are currently amended, appear in the application for the Examiner's consideration. The amendments to the claims 2-4 are made to correct typographical errors, and are supported by the original claims and the specification. As no new matter has been introduced, Applicants respectfully request that the amendments be entered at this time.

Election/Restrictions

In response to the Examiner's restriction requirement, Applicants confirm their election, with traverse, of the invention of Group I, claims 1-18; and the analog species number 8 of 10 in claim 15. It is believe that the Examiner has indicated the wrong peptide species. According to the office action (page 5 second paragraph), "the analog species number 8 of 10 in claim 15 [is] Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Phe-Gly(S2)-X". The analog 8 of 10 of original claim 15, however, is Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*Phe(N3)-X, and this peptide, known as 3205, is the one that applicants elect. This mistake may have arisen because claim 15 of the set of claims previously submitted inadvertently included the third and forth analogs in one row. This made it appear that the claim contained only 9 analogs and that the eighth analog selected was not the one intended. The correct species to be elected is: (Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3)-X).

Applicants respectfully submit that the inventions of Group I and Groups II-III are sufficiently related so that the restriction is improper. Although the process for using the product can be practiced with different peptide analogs, these products are not materially different from one another, evidenced by the fact that all the formulas and compounds are just variations in form of the same generic somatostatin analog recited in claim 1. For instance, all these analogs are based on the same novel structure (four to twelve amino acids with at least one building unit containing one nitrogen atom of the peptide backbone connected to a bridging group, where the building unit is connected via the bridging group to form a cyclic structure) and share the characteristics and advantages provided by this novel structure, including metabolic biostability and high affinity to a defined subset of somatostatin receptors (*see* specification, [0314]-[0318]). Thus, the method for treating disorders according to claims 19-21 and the method for diagnosing cancer according to claims 22-24 can only be practiced with the embodiments of the generic compound of claim 1, even when this generic

compound encompasses several formal variants, such that the inventions of Group I and Groups II-III are not sufficiently distinct from each other to warrant restriction.

Further, the methods of Groups II and III, while used for different effects, are not operationally distinct. They both use the same mode of operation, *i.e.*, administering a backbone cyclized somatostatin analog of claim 1 topically or systemically, including intravenous or intramuscular injections and nasal or oral ingestion (*see* specification, [0052]-[0053]). The fact that the compound prepared according to claim 1 can be used for different purposes and effects only emphasizes the usefulness and versatility of the present invention, and does not show that the methods are sufficiently different or independent inventions to require restriction.

Applicants respectfully disagree with the Examiner's statement that the inventions of Groups I-III require independent searches. Far from having acquired a separate status in the art as a separate subject for inventive effect, the inventions of all three Groups relate to somatostatin peptide compounds and the use of such compounds. Therefore, the search for each invention would be co-extensive, since all the art relating to somatostatin peptide compounds will have to be searched before a proper determination of patentability can be made, and Applicants believe that there would be no additional searching burden on the Examiner to review all current claims.

As to the species election requirement, Applicants elect, with traverse, the analog species number 8 of 10 in claim 15 (Phe(C3)-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3)-X). Applicants maintain that all the species in the application have fundamentally the same structure with shared characteristics and advantages as explained above (*see* specification, [0031]; [0045]-[0049]; [0309]-[0318]). Formed by incorporating novel building units with bridging groups attached to the alpha nitrogens of alpha amino acids, the different analogs are obvious variants of the same generic somatostatin analog of claim 1 and are not patentably distinct.

Accordingly, Applicants respectfully request that the inventions of Groups I-III be examined together and the patentability search be made on all pending claims without requiring restriction.

Information Disclosure Statement

Applicants note that an information disclosure statement and PTO Form 1449 were submitted on October 8, 2003. The requirements for information disclosure statement are therefore satisfied.

Claim Rejections – 35 U.S.C. § 112

Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention for the reasons set forth on pages 6-7 of the Office Action.

As to claim 2, Applicants note that the bridging group "Y" was not included in the claim due to an oversight. Claim 2 has now been amended to include the bridging group "Y" between the CO and $(CH_2)_n$ of Formula No. 7, as well as the definition for "Y," and is believed to meet the definiteness requirement under § 112. Claims 3 and 4 have also been amended to correct similar typographical oversight and now provide a definition for "Y" instead of "X."

With respect to claims 5 and 9-13, the confusion seems to have been caused by a typographical error. Specifically, "Y^2" is an error and should instead read "Y." This error, however, was corrected in the Preliminary Amendment submitted on June 19, 2003.

As to the Examiner's statement regarding claims 5 and 9-14, Applicants note that these claims were actually amended in the Preliminary Amendment submitted on June 19, 2003. The confusion may have been caused by the fact that the corrections made in these claims (changing "Y^2" to "Y") were minor and perhaps not clearly noticeable.

Since all the appropriate corrections are made and the ambiguities clarified, Applicants respectfully request that the § 112 rejections be withdrawn.

Claim Rejections -- 35 U.S.C. § 103

Claims 1-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Arad *et al.* in view of Kaljuste *et al.* for the reasons set forth on pages 7-8 of the Office Action. Applicants respectfully traverse.

Arad teaches the backbone cyclization technology of peptides and somatostatin analogs in general, but does not disclose attaching an amide, thioether, thioester, or disulfide

between the backbone amine nitrogens or including a non-cyclized chain of 4, 5 or 6 amino acids in the sequence. Kaljuste discloses a method for producing N-alkylated amino acids to a reduced peptide bond and, more specifically, N-building unit (disulfide) bridging group and a non-cyclized chain of four to six amino acids. While disclosing a non-cyclized chain of 4, 5 or 6 amino acids between cyclized residue, Kaljuste relates to peptides in general and does not teach cyclizing a somatostatin.

Therefore, while these two references teach the methods of carrying out backbone-cyclization and of producing disulfide bridging group and a non-cyclized chain of four to six amino acids, the references are too general and fail to include sufficient teachings to render the present invention obvious. In particular, these references fail to suggest backbone cylized peptides that are conformationally constrained somatostain analogs. Further, the novelty and unobviousness of the present invention is stressed by the difficulty in designing potent and biophysiologically useful somatostatin analogs that do not affect other known physiological activities of native hormone somatostatin. In fact, of the numerous backbone cyclized somatostatin analogs tested by the applicants, only a small number of peptide analogs as defined by the present claims were found to be active as somatostatin analogs. As such, the teachings of Kaljuste may be relevant for certain other analogs but would not lead one skilled in the art to design and select the specific compounds disclosed in the present application.

Rather, it appears that the Examiner is using improper hindsight in combining these two references. Without such hindsight, it would not be obvious to one skilled in the art to combine Arad with Kaljuste to come up with the somatostatin analogs of the present invention. Moreover, the specific compounds identified in the claims, such as PTR 3173 and the bi-cyclic analog PTR 3205, which have the highest activity, could not be suggested by either of the references, alone or in combination, as they incorporate further novel features such as octapeptide or bicyclic structures with receptor selectivity to certain defined SST subtypes (*see, i.e.*, specification, [0033]-[0040]).

Because the references neither suggest nor render obvious the novel backbone cyclized somatostatin analogs of the present invention, Applicants respectfully request that this claim rejection be withdrawn.

The Examiner also rejects claims 1-18 under 35 U.S.C. § 103(a) as being unpatentable over Arad *et al.* in view of Kaljuste *et al.* and Bauer *et al.* (U.S. Patent No. 4,395,403) for the reasons stated on pages 9-10 of the Office Action.

Bauer, however, does not teach or suggest backbone cyclization through N-alpha substituted amino acid but relates only to a simple S-S cyclization of peptide analogs. Although it relates to straight-chain and mono-cyclic peptides comprising a hexapeptide residue (*see* col. 1, lines 14-31), it does not teach cyclization by connecting a nitrogen atom of the peptide backbone to a bridging group comprising an amide, thioether, thioester or disulfide.

Providing only for the cyclization through the S of the same Cys residues (claims 13-15), the limited disclosure of Bauer fails to teach the advantageous designs for somatostatin analogs of the present invention, including, for example, connecting a nitrogen atom of the peptide backbone to a bridging group, and their potential benefits and uses. In fact, focusing only on the products formed by the simple S-S cyclization (col. 6, lines 29-37; col. 10-13, Examples 1A, 1B, 19-22), Bauer strengthens the inventiveness of the present application by emphasizing that it was unexpected to find the specific compounds of the present invention to be active. Hence, it would not be obvious to a person skilled in the art at the time of the invention to cyclize a specific-length somatostatin analog between two backbone amide nitrogen to design the compounds disclosed in the present application, because the prior art merely provides a general peptide cyclization technology and a very limited teaching of S-S cyclization that neither anticipates nor renders obvious the critical features of the present invention, which are characterized by novel building units with bridging groups attached to the alpha nitrogens of alpha amino acids. Such conformationally constrained backbone cyclization of somatostatin analogs provides many advantages over the prior art and presents clinical benefits, such as enhanced metabolic biostability and increased affinity to certain defined somatostatin receptors without affecting other known physiological activities of native hormonesomatostatin.

Accordingly, Applicants respectfully request that this § 103 rejection be withdrawn.

Double Patenting

The Examiner rejects claims 1-17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent Nos. 5,770,687; 6,051,554; and 6,355,613 B1.

These patents are, however, commonly owned parent applications of the present application. Hence, as the Examiner points out, a timely filed terminal disclaimer in

compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with the application. Further, effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. Accordingly, a terminal disclaimer has been prepared by the attorney of record and is filed with this response.

In view of the foregoing, it is believed that the application is now in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the claims. Please call the undersigned to expedite the allowance of all the claims in this application.

Respectfully submitted,

Date 2/23/04

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